CLAIMS

1. A method for preparation of microsphere, which comprises the following steps:

(a) emulsifying a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and an organic solvent having a boiling point lower than that of water into an aqueous solution in an emulsifying device to form an emulsion wherein said medicament-containing polymer solution is dispersed in the aqueous solution;

(b) transferring the obtained emulsion into a microsphere storage tank;

(c) introducing a part of the emulsion from the microsphere storage tank into a cross flow filter;

(d-1)-i) returning a liquid passing over the filter to the microsphere storage tank;

(d-1)-ii) recycling a filtrate filtered from the above cross flow filter as an aqueous solution for Step (a), repeating Steps (a) to (d-1), and when the organic solvent having a boiling point lower than that of water is immiscible with water, then evaporating said organic solvent in the microsphere storage tank during this circulation process; or

(d-2)-i) returning a liquid passing over the cross flow filter to the microsphere storage tank;

(d-2)-ii) discharging a filtrate filtered from the above cross flow filter without recycling it as the aqueous solution for Step (a), repeating Steps (a) to (d-2) with using a fresh aqueous solution, and when the organic solvent having a boiling point lower than that of water is immiscible with water, then evaporating said organic solvent in the microsphere storage tank during this circulation process;

(e) collecting microsphere in the microsphere storage tank after

Step (d-1) or (d-2) is completed.

2. The method according to claim 1, wherein the medicament-containing polymer solution is one of the following ones:

(i) a solution in which a biocompatible and biodegradable hardly-water-soluble polymer and a medicament are dissolved in an organic solvent having a boiling point lower than that of water;

(ii) a suspension in which a biocompatible and biodegradable hardly-water-soluble polymer is dissolved in an organic solvent having a boiling point lower than that of water, and a medicament is suspended in the resulting polymer solution;

(iii) a dispersion in which a biocompatible and biodegradable hardly-water-soluble polymer is dissolved in an organic solvent having a boiling point lower than that of water, and an aqueous solution of medicament is dispersed in the resulting polymer solution;

(iv) a dispersion in which one of biocompatible and biodegradable hardly-water-soluble polymers is dissolved in an organic solvent having a boiling point lower than that of water, and a solution of the other biocompatible and biodegradable hardly-water-soluble polymer in the same organic solvent is dispersed in the resulting polymer solution, and further a medicament is dissolved or suspended in the dispersed polymer solution.

3. The method according to claim 1 or 2, wherein the emulsification of Step (a) is carried out continuously, and the resulting emulsion is transferred continuously into the microsphere storage tank.

4. The method according to claim 1 or 2, wherein the emulsification of Step (a) is carried out by batch-treatment, and the resulting emulsion in each batch is transferred individually into the microsphere storage tank.

5. The method according to any one of claims 1 - 4, wherein the organic solvent having a boiling point lower than that of water is

immiscible with water, and the organic solvent having a boiling point lower than that of water is evaporated from an emulsion in the microsphere storage tank by warming, pressure reduction, blowing of a gas, evaporation with a hollow fiber membrane module, or a combination of these methods.

6. The method according to claim 5, wherein the organic solvent having a boiling point lower than that of water is evaporated from an emulsion in the microsphere storage tank by evaporation with a hollow fiber membrane module.

7. The method according to claim 6, wherein the organic solvent having a boiling point lower than that of water is a halogenated aliphatic hydrocarbon solvent.

8. The method according to any one of claims 1 to 4, wherein the organic solvent having a boiling point lower than that of water is miscible with water, and the evaporation of the organic solvent having a boiling point lower than that of water from an emulsion in a microsphere storage tank is not carried out.

9. The method according to claim 8, wherein the organic solvent having a boiling point lower than that of water is a water-miscible ketone solvent.

10. The method according to claim 8, wherein the medicament-containing polymer solution is one in which a medicament is suspended and a biocompatible and biodegradable hardly-water-soluble polymer is dissolved in a water-miscible organic solvent having a boiling point lower than that of water, and the aqueous solution is a uniform aqueous solution containing a solvent being immiscible with said water-miscible organic solvent but being miscible with water.

11. The method according to claim 1 or 2, wherein during Step (d-1) or Step (d-2), the filtration speed through the cross flow filter and the influx speed of the emulsion from the emulsifying device into the

microsphere storage tank are controlled substantially the same so as to keep the volume of the emulsion in said tank substantially constant.

12. The method according to claim 4, the capacity of the microsphere storage tank is 10 to 1000 times of that of the emulsifying device for batch-treatment.

13. The method according to any one of claims 1 to 12, wherein the pore size of the membrane filter of the cross flow filter is in the range of 1/300 to 1/3 of the average particle size of the desired microsphere, and the filtration speed of the filtrate from the cross flow filter is adjusted to the range of 1/100 to 1/3 of the introduction speed of the emulsion into said cross flow filter.

14. The method according to claim 13, wherein the pore size of the membrane filter of the cross flow filter is within the range of 0.01 to 10 μm.

15. The method according to any one of claims 1 to 14, wherein the emulsification is carried out by a high-speed rotary homogenizer utilizing inner shear (liquid-liquid shear).

16. The method according to any one of claims 1 to 15, wherein the emulsification in Step (a) is carried out using the aqueous solution in a volume of 1 to 1000 times of that of the medicament-containing polymer solution.

17. The method according to claim 1, wherein Step (d-1) is employed.

18. The method according to claim 1, wherein Step (d-2) is employed.

19. The method according to any one of claims 1 to 18, wherein the biocompatible and biodegradable hardly-water-soluble polymer is a polyester of hydroxyfatty acid.

20. The method according to any one of claims 1 to 19, wherein the microspheres are collected by dead-end filtration, cross flow filtration or centrifugation, or a combination of these methods.

21. The method according to claim 17, wherein the medicament is

recovered from the aqueous solution after the collection of the microspheres.

22. A method for preparation of lyophilized microsphere, which comprises preparing microspheres by the method as set forth in any one of claims 1 to 21, dispersing the microspheres thus obtained in an aqueous solution of an excipient if necessary, and then subjecting the resultant to lyophilization.

23. A lyophilized microsphere as prepared by the method as set forth in claim 22.

24. An apparatus for preparation of microsphere from a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and an organic solvent having a boiling point lower than that of water, and an aqueous solution in a closed system, wherein an emulsifying device, a microsphere storage tank and a cross flow filter are set up in the following manner:

(i) it has a structure by which a medicament-containing polymer solution and an aqueous solution can be introduced into the emulsifying device;

(ii) the emulsifying device and the microsphere storage tank are connected in such a manner that an emulsion obtained in the emulsifying device can be transferred into the microsphere storage tank having a function of evaporation of organic solvent;

(iii) the microsphere storage tank, the cross flow filter and the emulsifying device are connected in such a manner that a part of the emulsion contained in the microsphere storage tank is introduced into the cross flow filter, and a liquid passing over the cross flow filter is returned to the microsphere storage tank while a filtrate filtered through the cross flow filter is introduced into the emulsifying device as an aqueous solution.

25. The apparatus according to claim 24, wherein the function for evaporation of organic solvent of the microsphere storage tank is a function of evaporation with a hollow fiber membrane module.

26. An apparatus for preparation of microsphere from a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and an organic solvent having a boiling point lower than that of water, and an aqueous solution in a closed system, wherein an emulsifying device, a microsphere storage tank and a cross flow filter are set up in the following manner:

(i) it has a structure by which a medicament-containing polymer solution and an aqueous solution can be introduced into the emulsifying device;

(ii) the emulsifying device and the microsphere storage tank are connected in such a manner that an emulsion obtained in the emulsifying device can be transferred into the microsphere storage tank;

(iii) the microsphere storage tank, the cross flow filter and the emulsifying device are connected in such a manner that a part of the emulsion contained in the microsphere storage tank is introduced into the cross flow filter, and a liquid passing over the cross flow filter is returned to the microsphere storage tank while a filtrate filtered through the cross flow filter is introduced into the emulsifying device as an aqueous solution.

27. An apparatus for preparation of microspheres from a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and an organic solvent having a boiling point lower than that of water, and an aqueous solution in a closed system, wherein an emulsifying device, a microsphere storage tank and a cross flow filter are set up in the

following manner:

(i) it has a structure by which a medicament-containing polymer solution and an aqueous solution can be introduced into the emulsifying device;

(ii) the emulsifying device and the microsphere storage tank are connected in such a manner that an emulsion obtained in the emulsifying device can be transferred into the microsphere storage tank having a function of evaporation of organic solvent;

(iii) the microsphere storage tank and the cross flow filter are connected in such a manner that the emulsion contained in the microsphere storage tank is introduced into the cross flow filter, and a liquid passing over the cross flow filter is returned to the microsphere storage tank while a filtrate filtered through the cross flow filter is discharged outside of the apparatus.

28. The apparatus according to claim 27, wherein the function for evaporation of organic solvent of the microsphere storage tank is a function of evaporation with a hollow fiber membrane module.

29. An apparatus for preparation of microspheres from a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and an organic solvent having a boiling point lower than that of water, and an aqueous solution in a closed system, wherein an emulsifying device, a microsphere storage tank and a cross flow filter are set up in the following manner:

(i) it has a structure by which a medicament-containing polymer solution and an aqueous solution can be introduced into the emulsifying device;

(ii) the emulsifying device and the microsphere storage tank are connected in such a manner that an emulsion obtained in the emulsifying device can be transferred into the microsphere storage

tank;

(iii) the microsphere storage tank and the cross flow filter are connected in such a manner that the emulsion contained in the microsphere storage tank is introduced into the cross flow filter, and a liquid passing over the cross flow filter is returned to the microsphere storage tank while a filtrate filtered through the cross flow filter is discharged outside of the apparatus.

30. The apparatus according to any one of claims 24 to 29, wherein the capacity of the microsphere storage tank is in the range of 10 to 100 liters per 1 kg of the microspheres to be prepared in one production, as well as 10 to 1000 times of the capacity of the emulsifying device.

31. The apparatus according to any one of claims 24 to 30, which has a function of adjusting the filtration speed of the filtrate from the cross flow filter and the influx speed of the emulsion into the microsphere storage tank, and wherein the pore size of the membrane filter of the cross flow filter is in the range of 0.01 to 10 μm.